FILED ELECTRONICALLY

PATENT APPLICATION
Docket No. 16785.10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of		)
		)
	Seth Hallström et al.	)
		)
Serial No.:	10/599,401	) Art Unit
		) 1656
Filed:	February 27, 2007	)
		)
Conf. No.:	8352	)
		)
For:	PHARMACEUTICAL COMBINED PREPARATION CONTAINING A THERAPEUTIC PROTEIN	)
		)
Examiner:	Samuel W. Liu	)
		)
Customer No.:	022913	)

REQUEST FOR PRE-APPEAL BRIEF CONFERENCE AND PANEL REVIEW

Mail Stop APPEAL
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the final Office Action of March 16, 2011, and concurrent with the filing of a Notice of Appeal and a one-month extension of time, please consider the succinct, concise and focused set of arguments for which a pre-appeal brief conference and panel review is requested, which begin on the next page.

I. STATUS OF AFTER FINAL AMENDMENT

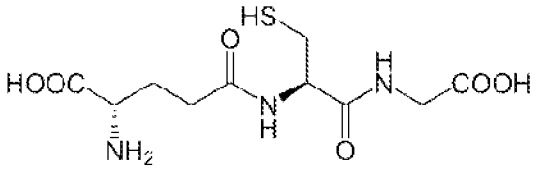
Applicants submitted an after final amendment on May 12, 2011. The amendment should have been entered under 37 CFR 1.116(b)(2) because it places the "claims in better form for consideration on appeal" and under MPEP 714.13(II) because it merely "adopts examiner suggestions, removes issues for appeal, or in some other way requires only a cursory review by the examiner". Claim 1 was only amended in the manner suggested by the Examiner during the Examiner Interview of April 26, 2011 to address a 112, ¶ 2 rejection. Applicants request review of claim 1 as amended or, in the alternative, agree to file a timely amendment to address the 112, ¶ 2 rejection in the event the 103 rejection is removed by the pre-appeal conference.

II. PRESENT INVENTION

The claims on appeal claim a method of treating of ischemia comprising administering a pharmaceutical preparation [to a subject in need thereof] comprising (i) a therapeutic protein having nitrosated SH-groups, wherein the therapeutic protein is S-nitroso albumin and (ii) reduced glutathione. Applicants discovered that administering the claimed narrow species of proteins provides unexpected and unpredictable therapeutic results, as explained in Examples 1-3 of the Application (*i.e.*, an unexpected and unpredictable drop in blood pressure (Example 1), an unexpected and unpredictable increase in nitric oxide (NO) release (Example 2), and an unexpected and unpredictable drop in platelet aggregation (Example 3)).

III. RESPONSE TO 103 REJECTION

Claims 1, 2, 7 and 14 stand rejected as being unpatentable over *Schlag* and *Hallström*. The Examiner commits clear error by failing to show that the claimed narrow species is *prima facie* obvious over *Schlag* and *Hallström* and/or by ignoring evidence of unexpected and unpredictable results. The narrow species of claim 1 is administering a composition comprising S-nitroso albumin and *reduced* glutathione to patient to treat ischemia (*i.e.*, insufficient supply of blood to an organ). Reduced glutathione has the following molecular structure:



http://en.wikipedia.org/wiki/Glutathione. Reduced glutathione has a single thiol group (-SH) bonded to a carbon atom, as shown in the molecular structure, but no S-nitroso group, as would be present if it were "nitrosated". Only S-nitroso albumin is "nitrosated".

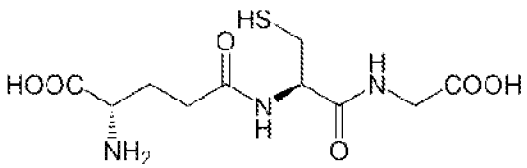
In rejecting the claims over *Schlag* and *Hallström* the Final Action interprets the relevant teachings of *Schlag* as follows:

> Schlag et al. teach a method of treating an ischemia (cerebral ischemia) comprising administering to a patient in need thereof a pharmaceutical composition comprising at least one (plurality) [see patent claim 16, line 4] thiol nitrosated (i.e., S-nitroso) thiol-goup-containing proteins, wherein 'at least one' encompasses more than one S-nitroso-proteins that include S-nitroso-albumin (patent claims 21). This is applied to instant claim 1….
>
> Schlag et al. do not expressly disclose or provide working example for combined use of S-nitroso-albumin (S-NO-HAS) and S-nitroso-glutathione (GSH) for treating ischemia.
>
> Schlag et et al., however, teach that the increased S-nitrosation level is companied with the higher the "NO-coupled effect" when administering a nitrosated protein preparation comprising said increased S-nitrosation level (col. 2, lines 23-34).

FA, pp. 3-4 (emphasis in original). The Examiner therefore argues that *Schlag* teaches the use of "more than one S-nitroso-protein" but does not explicitly teach the "combined use of S-nitroso-albumin (S-NO-HAS) and S-nitroso-glutathione (GSH) for treating ischemia". *Id.* Based on this understanding of *Schlag*, the Examiner asserts that the "combined use of S-nitroso-albumin (S-NO-HAS) and S-nitroso-glutathione (GSH) for treating ischemia" would be obvious in view of the combination of *Schlag* and *Hallström*. *Id.*

The Final Action is based on flawed logic. First, it mischaracterizes GSH as being "S-nitroso-glutathione". Second, it asserts that *Schlag* teaches the benefits of "increased S-nitrosation level" (*i.e.*, to an extent not provided by S-nitroso albumin by itself). Third, it asserts that it would have been obvious to combine GSH with S-Nitroso albumin to treat ischemia because to do so would provide the desired "increased S-nitrosation level" of *Schlag*. Fourth, it asserts that *Hallström* suggests administering GSH to treat ischemia. The Final Action can only state a *prima facie* case of obviousness if all four of the foregoing propositions is correct. If any is false, the rejection fails and the claims are not *prima facie* obvious over the cited art. In fact, at least three of the four propositions is manifestly false, which is clear error.

The first proposition that GSH is "S-nitroso-glutathione" is clearly erroneous because GSH does not contain S-nitroso groups. *See* http://en.wikipedia.org/wiki/Glutathione:



Because GSH is not in fact "S-nitroso-glutathione" and contains no S-nitroso groups, it cannot logically satisfy the third proposition of providing a therapeutic composition having "increased S-nitrosation level" compared to S-Nitroso albumin by itself.[1] For either of these two reasons, the Final Action fails to state a *prima facie* case of obviousness.

Moreover, the fourth and final proposition that *Hallström* suggests administering GSH to treat ischemia is also false. *Hallström* merely teaches that S-nitroso albumin reduces ischemia injury via NO release and that S-nitroso albumin, when administered to a patient, beneficially alters the ratio of GSH to GSSH already existing naturally in the body. *Hallström*, p. 3037, rt. col., ln. 17-26 (in "treatment groups" given S-NO-HSA (S-nitroso albumin), "[t]he concentration of GSH by far exceeds that of GSSH, which is effectively converted into GSH by the NADPH-utilizing enzyme glutathione reductase"). Because *Hallström* teaches that "GSSH is *effectively* converted into GSH" such that "[t]he concentration of GSH by far exceeds that of GSSH" when a subject is given S-nitroso albumin alone, there would have been no recognized reason to administer GSH *in combination with* S-nitroso albumin, as in the claimed methods.

The *2010 KSR Guidelines Update* published by the USPTO in the Federal Register explains that modifying the prior art in such a way as to require greater expenditure of "time, effort, or resources" is only obvious if the skilled artisan has a "recognized reason to do so". *See* 75 FR 53643, 53646 (Sept. 1, 2010). Specifically, the *2010 KSR Guidelines* state:

> KSR [] noted that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." KSR, 550 U.S. at 401. In view of the cases decided since KSR, one situation when it is important to identify a reason to combine known elements in a known manner to obtain predictable results is when the combination requires a *greater expenditure of time, effort, or resources* than the prior art teachings. Even though the components are known, the combining step is technically feasible, and the result is predictable, *the claimed invention may nevertheless be nonobvious* when the combining step involves such *additional effort* that no one of ordinary skill would have undertaken it *without a recognized reason to do so*.

Id. (emphasis added).

[1] Moreover, the Final Action fails show where *Schlag* teaches that S-Nitroso albumin fails to provide the desired "S-nitrosation level" and should be supplemented with GSH to provide "increased S-nitrosation level" (FA, p. 4). The only reference to GSH is when *Schlag* identifies proteins suitable for nitrosation and disparages "glutathione" as being a non-preferred "low-molecular protein[]" as opposed to the preferred "high molecular proteins" (*e.g.*, albumin). Col. 2, ln. 53-62 ("for the purposes of the present invention therapeutically usable proteins are preferred, … such as *albumin*…. According to the present invention, high-molecular proteins are preferred over low-molecular proteins, such as, e.g., *glutathione*") (emphasis added). Hence, the second proposition is also likely false.

In short, because *Hallström* teaches that S-nitroso albumin, when administered *by itself*, is highly effective in causing the body's own natural enzyme glutathione reductase to convert GSSH to GSH, there was no teaching, suggestion, motivation or other reason that would have prompted to skilled artisan to modify *Schlag* to administer *both* S-nitroso albumin *and* reduced glutathione to a patient suffering from ischemia. To do so would be redundant according to an objective reading of *Hallström*. Moreover, according to the *2010 KSR Guidelines Update*, administering both S-nitroso albumin and reduced glutathione to a patient suffering from ischemia would not have been obvious because it would require "a greater expenditure of time, effort, or resources" "without a recognized reason to do so" (*i.e.*, administering the correct dosages of two compounds requires greater expenditure of time, effort, or resources compared to administering one compound, and *Hallström* expressly teaches that S-nitroso albumin by itself causes the body's own enzyme (glutathione reductase) to create more GSH from GSSH).

In view of the foregoing, the Final Action fails to state a *prima case* of obviousness relative to the claimed invention because at least three of the four propositions upon which the rejection is based are false and clearly erroneous.

Moreover, the Advisory Action fails to adequately respond to Applicants' arguments in the after final amendment pointing out that the combination of *Schlag* and *Hallström* fails to teach or suggest administering the specific combination of S-nitroso albumin and *reduced* glutathione to a patient suffering from ischemia. The Examiner argues in the Advisory Action that "[t]he claim 1 open-ended language 'comprising' allows for said 'plurality' of S-nitroso protein(s)". However, Applicants never argued that claim 1 excludes S-nitroso proteins besides S-nitroso albumin, only that the prior art fails to teach or suggest the combination of S-nitroso albumin and *reduced* glutathione. The assertion that *Schlag* suggests using a plurality of S-nitroso proteins would not lead one or ordinary skill in the art to use reduced glutathione, which is not an S-nitroso protein, but rather is a teaching away from using GSH. And to the extent *Schlag* teaches using a plurality of S-nitroso proteins, such proteins are two or more of albumin, orosomucoid, plasminogen-activator, tissue-plasminogen activator, fibrinogen, Lys-plasminogen, and hemoglobin, not albumin and glutathione. *See* col. 2, ln. 53-62 ("proteins … such as albumin, orosomucoid, plasminogen-activator (e.g. tissue-plasminogen activator), fibrinogen, Lys-plasminogen or hemoglobin or also *mixtures of* ***such*** *proteins* nitrosated or capable of being nitrosated according to the invention [are] particularly preferred" and that such "high-molecular proteins are preferred over low-molecular proteins, such as, e.g., glutathione") (emphasis added).

Finally, Examples 1-3 of the Application (¶¶ 62-76) describe unexpected results when administering S-nitroso albumin and reduced glutathione compared to administering S-nitroso albumin alone. During the Examiner Interview of April 26, 2011, the Examiner's supervisor, Anand Desai, acknowledged that a showing of unexpected results when using the claimed combination compared to using S-nitroso albumin by itself should be sufficient to rebut *prima facie* obviousness (to the extent it exists). Example 1 demonstrated a drop in blood pressure when S-nitroso albumin was administered together with reduced glutathione compared to administering S-nitroso albumin alone. Example 2 demonstrated an increase in NO release when S-nitroso albumin was administered together with reduced glutathione compared to administering S-nitroso albumin alone. Example 3 demonstrated a drop in platelet aggregation when S-nitroso albumin was administered together with reduced glutathione compared to administering S-nitroso albumin alone. The Advisory Action fails to adequately address the unexpected results but simply asserts (erroneously) that "GSH is a compound *routinely used* … for treatment of ischemia" as taught by *Schlag* and *Hallström*. Simply repeating the alleged *prima facie* case does not address, and is insufficient to explain and therefore fails to rebut, the unexpected results.

And in event, *Schlag* only discloses glutathione in the context of "nitrosated" (not reduced) proteins (col. 2, ln.53-62), thus teaching away from using "reduced glutathione" instead of "nitrosated glutathione", and *Hallström* only teaches that administering S-nitroso albumin causes the body's own natural enzyme glutathione reductase to "effectively" convert GSSH, which is already present in the body, to GSH. Neither suggests giving GSH to a patient to treat ischemia or that GSH would provide any recognized benefit beyond that provided by S-nitroso albumin. And even if some unidentified benefit could be inferred, *Schlag* and *Hallström* clearly do not show the unexpected results described Examples 1-3 of the Application, which are objective evidence of non-obviousness.

Dated this 18th day of July 2011.

Respectfully submitted,

/John M. Guynn 36153/

JOHN M. GUYNN
Registration No. 36,153
WORKMAN NYDEGGER
Customer No. 022913

JMG:jb
3418375_1